REMARKS

Restriction Requirement

Applicant hereby elects Group I, claims 28-35 and 59-61, drawn to methods of hybridization in which probe linkers are used, without traverse. With regards to sequence election, Applicant hereby provisionally elects SEQ ID No. 76, with traverse.

Status of the claims and claim amendments

Claims 1-27, 36-37 and 40-57 were canceled. Claims 28-35, 38-39 and 58-61 are pending and are subject to restriction requirement. Claims 28-35 and 59-61 are elected. Claims 38-39 and 58 are canceled herein. Claims 28, 34, 59 and 61 are amended herein. No new matter is added to the amended claims.

Claim 28 is amended to include colon (:) after comprising in step (b) of the claim. Claim 34 is amended to correct the claim language and include "the" before second reporter linker. Claim 59 is amended to include TA sequences within the probe linker sequence as well as the overlap linker sequence since this was the design and practice of the probes as described. The TA sites facilitate interstrand crosslinking during manufacture or use of the probes and reporters. All pairs of probe and reporter linkers as previously described were designed with and include five TA sites to enable psoralen plus UV interstrand crosslinking. The linker sequences of Claim 61 all have five TA sites within their sequence. Claim 61 is amended to include sequences of the reporter linkers having SEQ ID Nos. 12, 73, 78 and 83 that are complementary to the previously claimed sequences having SEQ ID Nos. 10, 71, 76 and 81 respectively.

The Examiner states that the sequences are patentably distinct since they are unrelated and searching for these sequences in the database would put an undue burden on the Examiner and office resources. Applicant respectfully disagrees with the Examiner.

The instant invention is directed to methods of detecting the presence of a polynucleotide sequence using probes that combine the signal strength of longer DNA probes with the specificity and ease of manufacture of short oligonucleotide probes. One such method involved the use of a nucleic acid probe that has a probe linker at each of the two ends of the probe unit. This probe unit was synthesized as two overlapping oligonucleotides. The primary probe subunit oligonucleotide has a sequence complementary to the single stranded target nucleotide sequence in the middle flanked by a first linker sequence complementary to a reporter unit on one end and an overlap linker on the other end. Small sets of spacer bases are optionally included in the primary probe to facilitate hybridization between the oligonucleotide sequences. The secondary probe subunit lacks target sequence but has overlap linker at its 3' end and has a second linker sequence complementary to a reporter unit at its 5' end. These subunits are typically joined and crosslinked together prior to probe use. Thus in brief, the resulting composite probe described herein has a sequence complementary to target sequence in the central region and each terminal region contains a probe linker sequence for a reporter attachment or attachment of a multilinking subunit (to bind multiple reporters). Both the 5' and 3' end linker sequences can be interstrand crosslinked using psoralen plus UV crosslinking and these sequences are specifically designed to enable the formation of three to five such interstrand crosslink sites within the 12-27 base pair lengths of the overlap linker or reporter linker sequences (a 5' TA site can be interstrand crosslinked with psoralen and UV by covalently joining adjacent thymidine bases on opposite strands). (page 27, line 24- page 28, line 22; figs. 3A-C).

As discussed *supra*, each of the linker sequences that were developed for the double-linker probe and reporter systems of the instant invention carry up to five spaced out 5'TA sites for psoralen plus UV interstrand crosslinking. These linkers with their crosslinking capacity are central to the design of the probe and reporter system of the instant invention in that they provide modular joining and binding between different target-specific probes and different generic reporter

units which differ in size and/or signaling color. The central importance of the different claimed probe/reporter linker sequences is further evidenced in comparing the linkers required and illustrated for the practice of Claims 32/33 vs. Claim 34: The instant invention teaches that in a reporter array of Claim 32/33, one linker pair is used for all connections; the probe linker is complementary to the proximal reporter linker and the distal reporter linker is the same as the probe linker. Thus each distal linker is the same as the probe linker and such reporters could make an infinite chain of identical reporters unless a terminator oligonucleotide (Claim 33) is provided to end this structure. In contrast, the instant invention teaches that the reporter sets of Claim 34 employ two pairs of complementary linkers to make reporters of two forms Type I and II. Type I has a proximal linker complementary to the probe linker and a distal linker of a different linker pair. The Type II reporter has a proximal linker complementary to the distal linker of the Type I reporter and a distal linker that will bind another Type I reporter. Consequently, Type I and Type II reporters can be added sequentially to a bound probe in order to add reporters in successive layers that alternate between Type 1 and Type II. The multiple paired sets of complementary linker sequences that are claimed are thus integral to the design and practice of the instant invention.

With regards to the reporters used in the probe, the instant invention teaches that these reporters are long segments of labeled double-stranded DNA (100-800 bp) with short single-stranded tails (20-30 bp) on one or both ends to serve as linkers (page 29, lines 13-18). The reporter linkers are complementary to the probe linkers described *supra* and they constitute a matching set of such linkers that enable simultaneous use of two or more different color or different size reporters with two or more different target-specific probes (figs. 4B, 7-13). Furthermore, the linkers were designed so that the probes or the reporters might not join non-specifically to unintended targets in the sample via any chance sequence matches that may occur with the linkers employed. Since the specification teaches that these reporters may comprise a set of linkers namely,

proximal and distal linkers (Example 3, Example 12, Figure 10), Applicant submits that the amended claim 61 complies with the teachings of the specification. Additionally, Applicant submits that applications involving use of such short sequence segments for identifying and detecting gene segments, for siRNA interference therapy or related diagnostic and therapeutic purposes are being routinely examined by USPTO and require comparing any of the claimed sequences to sequences that have been disclosed in prior applications. Hence, Applicant contends that a similar search for the short single-stranded polynucleotide sequences of the reporter linkers of the instant invention that are similar in design, function and in some cases complementary to each other will not pose a serious burden either on the Examiner or the office resources. Accordingly based on the above-mentioned remarks, Applicant respectfully requests the examination of Group I, claims 28-35 and 59-61 and reporter linker sequences having SEQ ID Nos. 6, 10, 12, 71, 73, 76, 78, 81 and 83.

Pursuant to 37 C.F.R. §1.136(a), Applicant hereby petitions that the period for response to the Restriction Requirement in the above-referenced patent applciation mailed April 11, 2005, in the above-referenced patent application, be extended for two (2) months to and including September 11, 2005. Please charge the $ 225.00 in fees under 37 C.F.R. §1.17(a) & (b) to the credit card identified on the attached form PTO-2038.

Respectfully submitted,

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